

Preparation of new type of organocatalysts having a carbohydrate scaffold^{1§}

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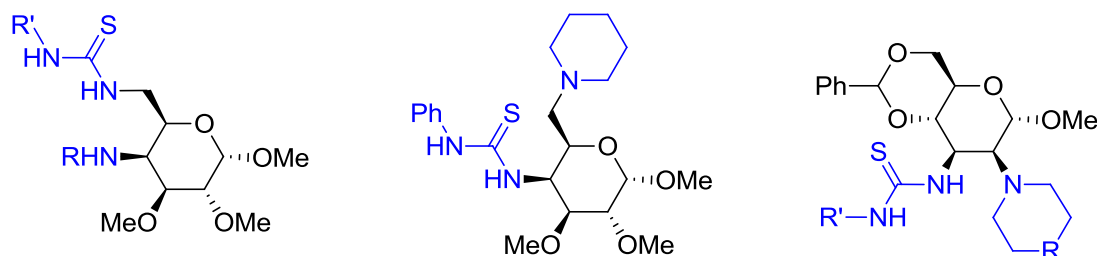
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ABSTRACT

The synthesis of nine new, bifunctional organocatalysts having carbohydrate scaffolds has been accomplished. In these catalysts both of the catalytic amino and thiourea functions are directly attached to a carbohydrate core. The activities of the newly prepared catalysts were tested in a Michael addition.

Graphical abstract



Keywords

Bifunctional organocatalysts, thiourea-amine type catalysts, carbohydrate scaffold, Michael addition

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1. Introduction

In recent years, organocatalysis, the acceleration of various chemical reactions by catalytic amounts of organic molecules, emerged as one of the rapidly developing areas of organic chemistry.¹ With the aid of organocatalysis a large number of chemical reactions could then be performed in stereoselective manner. Particularly great attention has been paid to the development of new, efficient catalysts. A special class of these catalysts is the so called bifunctional organocatalysts in which H-bond donor and Lewis base functionalities are combined in a single asymmetric molecular scaffold. Several different bifunctional catalysts have been designed, synthesized and tested. Most of these molecules have a combination of thiourea and amine groups as catalytic functionalities which are presented on a single chemical entity. The very first example of these catalysts has been described by Takemoto² in this molecule the catalytic centers are connected to a cyclohexane scaffold (compound **A**, Figure 1). Later some different chiral scaffolds such as binaphthyl³ or cinchona alkaloid⁴ (compounds **B** and **C**, Figure 1) were investigated and the catalysts based on these scaffolds showed promising results in asymmetric synthesis, particularly, in catalyzing Michael and aza-Henry reactions.

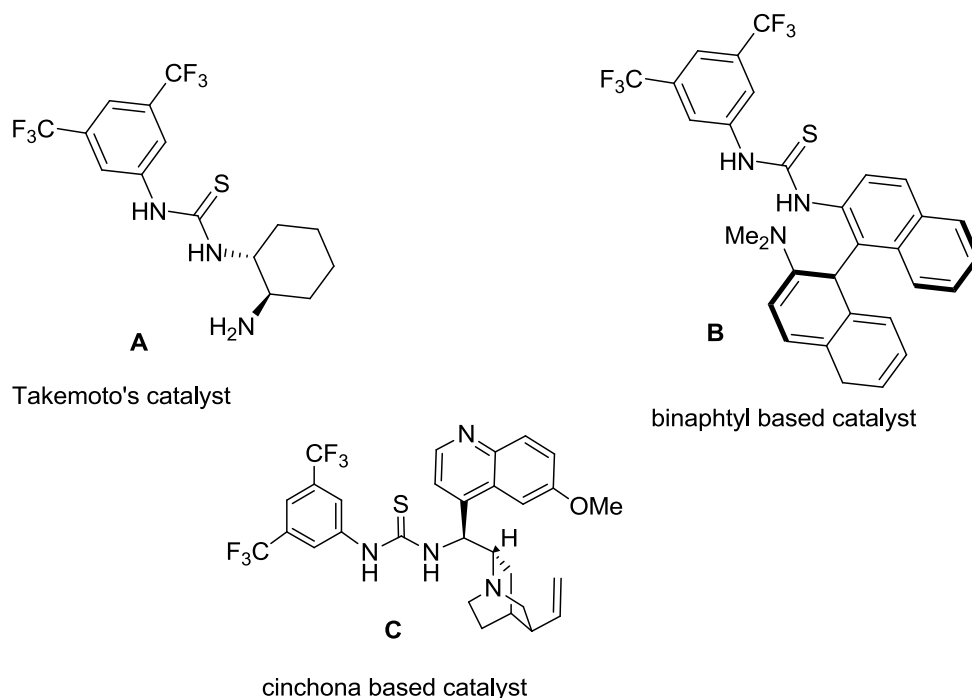


Figure 1. Representative examples of bifunctional organocatalysts

To date only a limited number of scaffolds has been used to synthesize bifunctional organocatalysts. Monosaccharides as commercially available, inexpensive molecules of

diverse chirality can be considered as obvious candidates for chiral scaffolds. Organocatalysts based on a D-glucosamine scaffold carrying urea and imine as catalytic functionalities were described by Kunz in 2007.⁵ Enantioselective Strecker and Mannich reactions were performed using these catalysts.⁵

Thiourea-amine type bifunctional organocatalysts containing a monosaccharide unit were prepared and their catalytic activities were investigated recently.⁶ In these cases, the carbohydrate moiety was located on the periphery of the catalyst molecule and not in-between the two catalytic centers (compounds **D** and **E**, Figure 2). To our knowledge there is only one example in the literature where a monosaccharide residue was used as a scaffold to connect thiourea and amine functionalities thereby defining the selectivity of the catalyzed reaction (compound **F**, Figure 2).⁷ In this study the use of urea derivatives, however, provided higher yields and selectivity than the corresponding thiourea derivative.⁷ Up to now, there are no examples of bifunctional thiourea-amine organocatalysts where the core scaffold is a monosaccharide unit and the use of the catalyst results in high yield and high enantioselectivity catalyzing a chemical reaction.

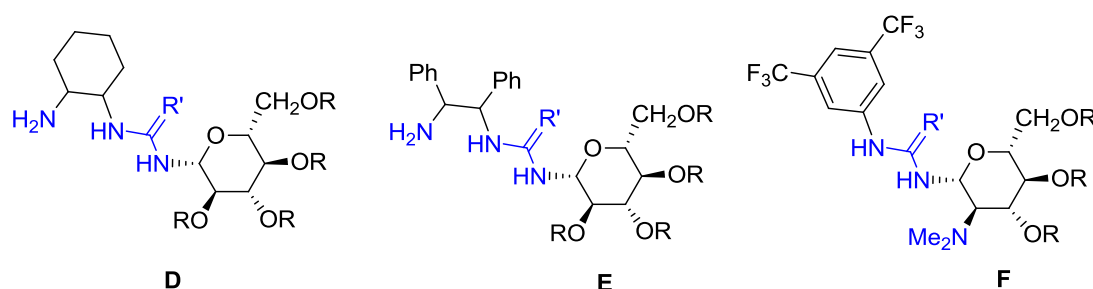


Figure 2. Monosaccharide-containing bifunctional organocatalysts

We have initiated the preparation of new - bifunctional - thiourea-amine catalysts starting from D-glucose. In these molecules the two catalytic centers are connected with a carbohydrate residue. Using these catalysts the enantioselectivity of the catalyzed reaction will be influenced only by the carbohydrate moiety. The possible effect arising from carbohydrate chirality was taken into consideration in the design, by placing the catalytic groups at various positions of the carbohydrate scaffold. Thus the synthesis of molecules having the amino and thioureido groups in positions 4 and 6 (**G** and **H**, Figure 3), or in positions 2 and 3 (**I**, Figure 3), respectively, was planned. The catalytic groups are distanced by three carbon-carbon bonds in the first case, whereas they are separated by two C-C bonds in the latter. In the case of **G** and **H**, the synthetic route was designed to afford both the 4-

amino-6-thioureido (**G**) and the 6-amino-4-thioureido (**H**) derivatives from the same starting material.

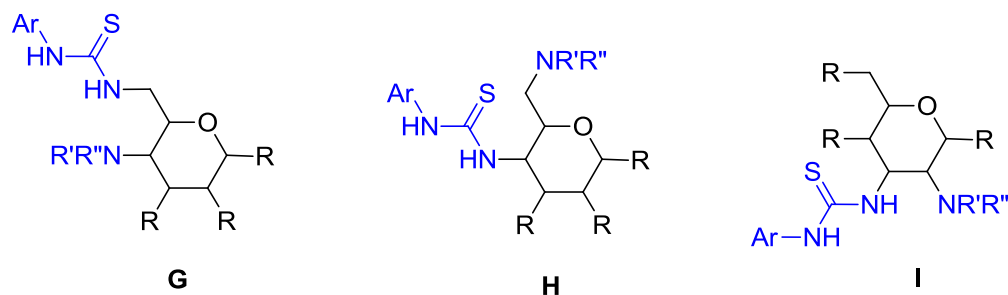
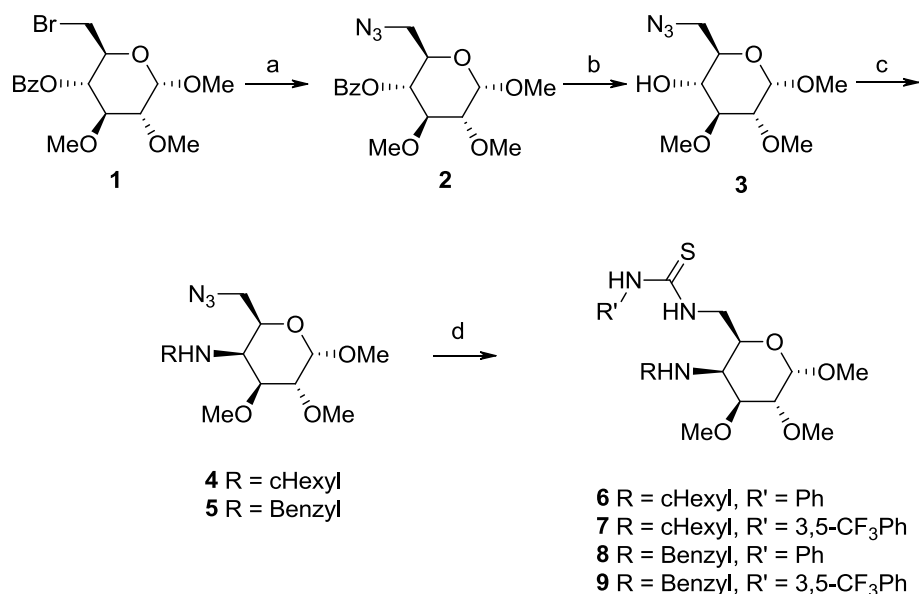


Figure 3. General structures of the targeted organocatalysts

2. Results and discussion

For the preparation of the targeted catalysts having the catalytic groups in the 4 and 6 positions, methyl 4-*O*-benzoyl-6-bromo-6-deoxy-2,3-di-*O*-methyl- α -D-glucopyranoside⁸ (**1**, Scheme 1) was selected as starting material which is easily available from commercial methyl α -D-glucopyranoside in a few steps in high yields.

The synthesis of the 4-amino-6-thioureido type compounds started with the preparation of the 6-azido derivative (**2**). Reaction of compound **1** with sodium azide in DMF at elevated temperature resulted in the formation of the 6-azido derivative (\rightarrow **2**, Scheme 1) in almost quantitative yield. The benzoate protecting group from compound **2** was removed with NaOMe in MeOH affording derivative **3** in high yield. 4-Amino derivatives were prepared by S_N2 replacement with primary amines *via* the 4-*O*-triflate in a one-pot manner. Treatment of **3** with triflic anhydride in CH_2Cl_2 in the presence of pyridine at 0 °C afforded the crude 4-*O*-triflate, which was reacted directly with cyclohexylamine or benzylamine in the solvent mixture of CH_2Cl_2 /DMF to yield the 4-cyclohexylamino (**4**) and 4-benzylamino (**5**) derivatives, respectively. The azido function of compound **4** was reduced to amine with propanedithiol in methanol⁹ and the 6-amino derivative was reacted with phenyl isothiocyanate (**4** \rightarrow **6**) or 3,5-bis(trifluoromethyl)phenyl isothiocyanate (**4** \rightarrow **7**) affording the bifunctional organocatalyst candidates.



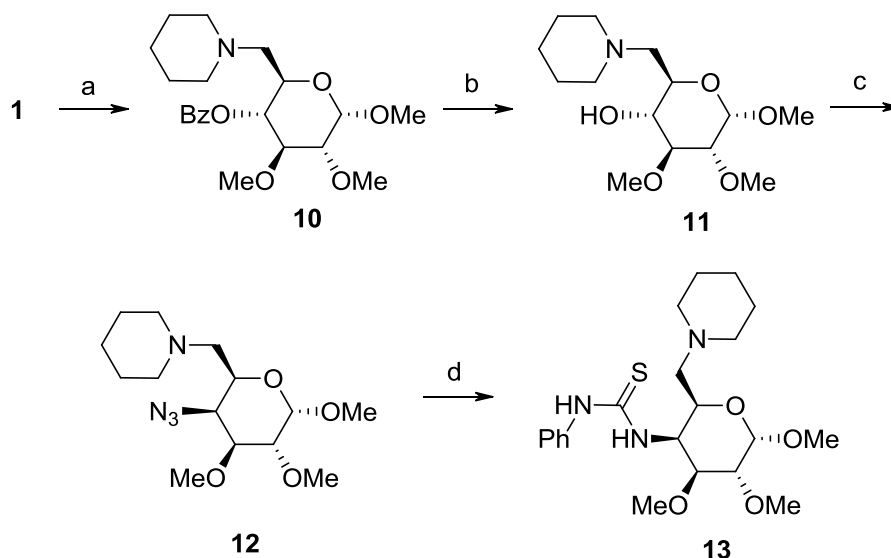
Scheme 1.

Conditions: a.) NaN₃, DMF, 70 °C, 6 h, 94%; b.) NaOMe, MeOH, rt., 1 h, 80%; c.) i: Tf₂O, pyridine, CH₂Cl₂, 0 °C, 2 h, ii: amine, DMF, 45 °C, 10 h, 50-70%; d.) i: propanedithiol, MeOH, rt., 48 h (**6** and **7**), or PPh₃, H₂O, THF, 80 °C, (**8** and **9**) ii: isothiocyanate, MeOH, rt., 4 h, 30-50%.

For the reduction of azido function of compound **5**, the use of triphenylphosphine was found more advantageous, as reduction with propanedithiol resulted in impurities which were difficult to separate from the amino derivative. The amino derivative of compound **5** was reacted with phenyl isothiocyanate or 3,5-bis(trifluoromethyl)phenyl isothiocyanate affording derivatives **8** and **9**, respectively.

For the preparation of the 6-amino-4-thioureido type target molecule nucleophilic substitution of the bromo function of compound **1** with piperidine was performed to afford **10** in high yield (Scheme 2). This reaction was significantly slower than the substitution of **1** with sodium azide. The removal of the benzoate protecting group from **10** by Zemplén's method required elevated temperature, but afforded compound **11** in good yield. The azido function was introduced at position **4** by S_N2 reaction *via* a triflate intermediate. Treatment of **11** with Tf₂O, as described for **4**, followed by reaction of the crude with sodium azide in DMF afforded the 4-azido *galacto* epimer (**11**→**12**). The stereochemistry was proven by the two small coupling constant of the H-4 in the ¹H-NMR spectrum (*J*_{3,4} 2.3 Hz *J*_{4,5} <1 Hz,) while the presence on the azido group was indicated by the upfield shift of the C-4 signal in the ¹³C NMR spectrum. The transformation of the azido function into thiourea derivative was

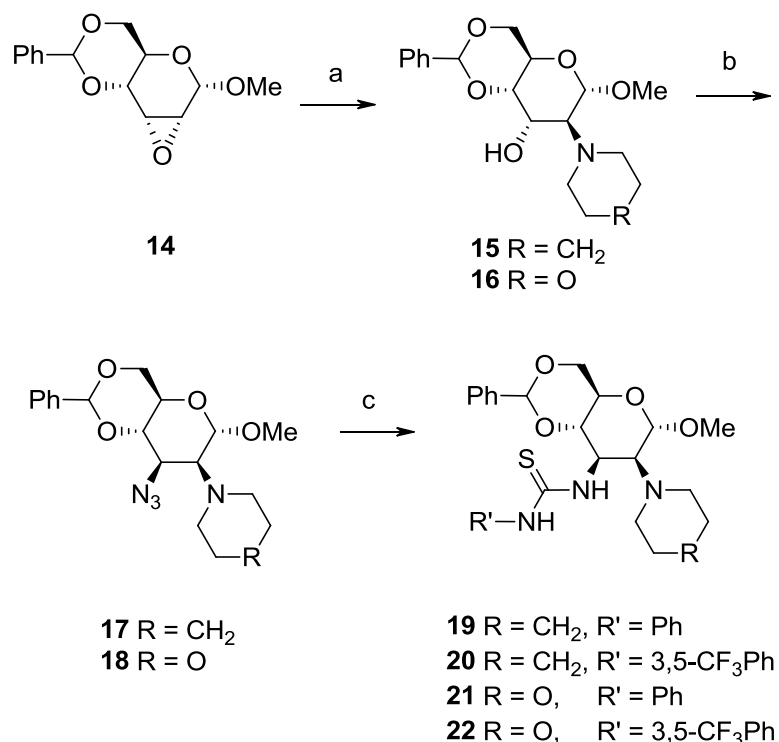
performed as in the case of compound **6**. Treatment of **12** with propanedithiol resulted in the formation of the 4-amino intermediate which was reacted with phenyl isothiocyanate to form compound **13** as a catalyst candidate.



Scheme 2.

Conditions: a.) piperidine, DMF, 70 °C, 50 h, 90%; b.) NaOMe, MeOH, reflux, 2 h, 85%; c.) i: Tf₂O, pyridine, DCM, 0 °C, 2 h, ii: NaN₃, DMF, 45 °C, 72 h, 40%; d.) i: propanedithiol, MeOH, rt., 48 h, ii: phenyl isothiocyanate, MeOH, rt., 8 h, 69%.

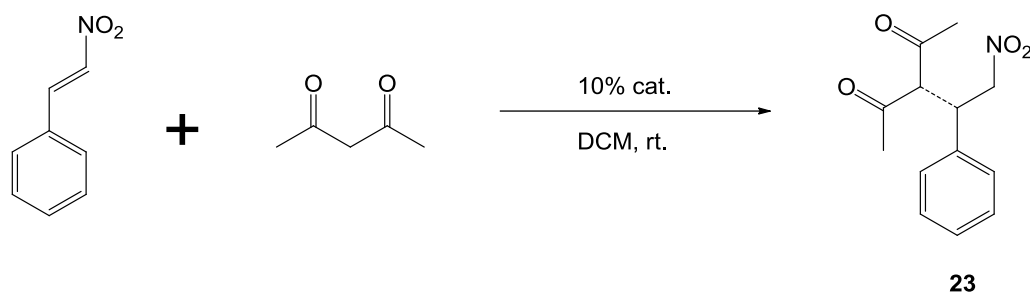
The preparation of the 2-amino-3-thioureido derivatives started from the *allo*-epoxide **14**¹⁰ (Scheme 3) as starting material which is easily available from commercial methyl α -D-glucopyranoside in a few steps in high yields. The epoxide was opened with piperidine or with morpholine according to a literature procedure¹¹ affording the *altro* derivatives **15** and **16** in high yields. The preparation of the 3-azido derivatives was accomplished by using Mitsunobu conditions as only low yields were obtained in preliminary trials to introduce the azide by the displacement of the 3-*O*-triflate intermediate (data not shown). Compounds **15** and **16** were treated with diisopropyl azodicarboxylate and triphenylphosphine then with diphenylphosphoryl azide¹² to form the 3-azido derivatives **17** and **18**, respectively. The azido functions of compounds **17** and **18** were reduced with triphenylphosphine, the resulting 3-amino derivatives were subsequently treated with phenyl isothiocyanate or 3,5-bis(trifluoromethyl)phenyl isothiocyanate affording the target compounds (**17**→**19**, **17**→**20**, **18**→**21** and **18**→**22**).



Scheme 3.

Conditions: a.) piperidine or morpholine, LiClO₄, MeCN, 90 °C, 24 h, 80-90%; b.) i: PPh₃, DIAD, THF, 0 °C, ii: DPPA, THF, rt., 24 h, 60-80%; c.) i: PPh₃, THF, H₂O, 80 °C, ii: isothiocyanate, MeOH, rt., 8 h, 60-80%.

The catalytic activity of the prepared new, monosaccharide-based bifunctional organocatalysts was tested on the Michael addition of acetylacetone to β-nitrostyrene (→**23**, Scheme 4). This reaction is commonly used as test in evaluating newly developed organocatalysts.¹³ Based on preliminary experiments dichloromethane was selected as solvent for the reaction. The use of other solvents such as toluene, THF, MeCN, or diethyl ether resulted in much longer reaction times (data not shown). The stereochemistry of the products was determined by comparison of their optical rotation values (Table 1) with literature references^{13c} together with the comparison of the chiral HPLC retention times with literature references.^{13d,e} The enantiomeric excess was determined by chiral HPLC.



Scheme 4.

Conditions: β -nitrostyrene, 1.1 eq. acetylacetone, 10 mol% catalyst, CH_2Cl_2 , rt., 24 h.

The catalytic activity of the synthesized compounds is summarized in Table 1. Only those compounds which have secondary amine groups were able to promote the reaction to give good yields (Table 1, entries 1, 2, and 3). Tertiary amine-containing derivatives afforded very low yield or no reaction at all (entries 4, 5, and 6). The active catalysts favored the formation of the product having the S configuration, the enantioselectivity, however, was low. Further examination of the catalytic activity of prepared compounds on different reactions is in progress, and will be reported in due course.

Table 1. Summary of the catalytic activity of selected catalyst candidates.

Entry	catalyst	Yield ^a	ee%	$[\alpha]_D^{25}$ values
1	6	70%	18.7%	13.9 (<i>c</i> 0.5, CHCl_3)
2	7	78%	14.1%	8.0 (<i>c</i> 0.5, CHCl_3)
3	9	50%	12.9%	7.8 (<i>c</i> 0.65, CHCl_3)
4	19	<5%	n.d.	n.d.
5	20	none	-	-
6	21	none	-	-

n.d.: not determined; ^a Reaction times were 24 h in all cases. Without the use of catalyst no product formation was observed.

In conclusion, the synthesis of a new family of monosaccharide-based bifunctional organocatalysts has been achieved. Thiourea and amine functionalities were used as catalytic centers connected by a monosaccharide unit thereby replacing the commonly employed cyclohexane unit. The activities of the newly prepared catalysts were tested on a model

reaction, where some of the compounds afforded high yields, although with low enantioselectivity.

3. Experimental

3.1. General. — Commercially available starting materials were used without further purification. Solvents were dried according to standard procedures. Melting points (uncorrected) were determined on a Griffin apparatus. Optical rotations were measured with a Jasco-Optical activity AA-10R polarimeter. NMR spectra were recorded on a Varian Gemini 2000 (200 MHz for ^1H and 50 MHz for ^{13}C) and on a Varian Unity-Inova (300 MHz for ^1H and 75 MHz for ^{13}C) spectrometer in CDCl_3 as solvent. All chemical shifts are quoted in ppm downfield from the characteristic signals (^1H : 0.00 ppm (TMS), ^{13}C : 77.00 ppm (CDCl_3)). Kieselgel 60 (E. Merck, Darmstadt, Germany) was used for column chromatography and DC-Alufolien Kieselgel 60 F₂₅₆ plates were used for TLC. MS spectra were recorded on an Applied Biosystems 3200 QTRap spectrometer. Enantiomeric excesses were determined on a Waters 600 HPLC instrument. (Diacel Chiralpack AD column, hexane:*i*-propanol 80:20, flow rate: 1 mL/min, $\lambda = 210$ nm).

3.2. Methyl 6-azido-4-*O*-benzoyl-6-deoxy-2,3-di-*O*-methyl- α -D-glucopyranoside (2)

NaN_3 (260 mg, 4.0 mmol) was added to a solution of **1** (780 mg, 2.0 mmol) in dry DMF (10 mL) and the mixture was stirred for 6 h at 70 °C. The mixture was allowed to cool to r.t. then it was diluted with EtOAc (100 mL) and washed with water (3×50 mL). The organic layer was dried over MgSO_4 , filtered, concentrated and the product was obtained after column chromatography (toluene–acetone; 95:5) as a syrup (660 mg, 94%). $[\alpha]_D^{25}$ 52.5 (*c* 0.69, CHCl_3); ^1H NMR: δ 8.06, 7.60, and 7.46 (m, 5 H, aromatic), 5.09 (dd, 1 H, $J_{3,4}$ 9.4 Hz, $J_{4,5}$ 9.9 Hz, H-4), 4.93 (d, 1 H, $J_{1,2}$ 3.5 Hz, H-1), 3.99 (ddd, 1 H, $J_{5,6}$ 5.4 and 2.6 Hz, H-5), 3.74 (dd, 1 H, $J_{2,3}$ 9.2 Hz, H-3), 3.56, 3.52 and 3.48 (each s, each 3 H, 3 OMe), 3.38 (m, 2 H, H-2 and H-6a), 3.27 (dd, 1 H, J_{gem} 13.3 Hz, H-6b); ^{13}C NMR: δ 165.4 (C=O), 133.4, 129.8, 129.3, and 128.5 (aromatic), 97.6 (C-1), 81.3 (C-2), 80.7 (C-3), 71.8 (C-4), 69.2 (C-5), 61.0, 59.3 and 55.5 (3 OMe), 51.3 (C-6); MS: Calcd. for: $\text{C}_{16}\text{H}_{21}\text{N}_3\text{O}_6$ 351, found: 352 $[\text{M}+\text{H}]^+$, 374 $[\text{M}+\text{Na}]^+$, 725 $[2\text{M}+\text{Na}]^+$. Anal. Calcd for $\text{C}_{16}\text{H}_{21}\text{N}_3\text{O}_6$: C, 54.69; H, 6.02. Found: C, 54.82; H, 6.05.

3.3. Methyl 6-azido-6-deoxy-2,3-di-*O*-methyl- α -D-glucopyranoside (**3**)

NaOMe (50 mg) was added to a solution of **2** (660 mg, 1.88 mmol) in dry MeOH (20 mL). The mixture was stirred for 1 h at rt. Then the mixture was neutralized with Amberlite IR-120 (H⁺). The resin was filtered off and washed with MeOH. The filtrate was concentrated and the product was isolated by column chromatography (toluene–acetone; 4:1). **3** (370 mg, 80%) was obtained as a colorless syrup: $[\alpha]_D^{25}$ 117.0 (*c* 0.58, CHCl₃); ¹H NMR: δ 4.81 (d, 1 H, *J*_{1,2} 3.5 Hz, H-1), 3.70 (m, 1 H, H-5), 3.60, 3.46 and 3.41 (each s, each 3 H, 3 OMe), 3.50 (dd, 1 H, *J*_{gem} 13.2 Hz, H-6a), 3.44–3.30 (m, 3 H, H-3, H-4 and H-6b) 3.20 (dd, 1 H, *J*_{2,3} 9.2 Hz, H-2) 2.18 (bs, 1 H, 4-OH); ¹³C NMR: δ 97.3 (C-1), 82.6 (C-3), 81.7 (C-2), 70.4 and 70.3 (C-4 and C-5), 61.1, 58.4 and 55.3 (3 OMe), 51.4 (C-6); MS: Calcd. for: C₉H₁₇N₃O₅ 247, found: 270 [M+Na]⁺, 517 [2M+Na]⁺. Anal. Calcd for C₉H₁₇N₃O₅: C, 43.72; H, 6.93. Found: C, 43.67; H, 6.95.

3.4. Methyl 6-azido-4-cyclohexylamino-4,6-dideoxy-2,3-di-*O*-methyl- α -D-galactopyranoside (**4**)

A solution of Tf₂O (1.63 mL, 9.7 mmol) in CH₂Cl₂ (5 mL) was added to a solution of **3** (1.61 g, 6.7 mmol) in a mixture of pyridine (3.2 mL) and CH₂Cl₂ (20 mL) at 0 °C, then the mixture was stirred for 2 h at 0 °C. TLC (hexane–EtOAc; 1:1) showed the formation of a new apolar derivative. Cyclohexylamine (6 mL) in DMF (20 mL) was added to the mixture and stirring was continued for 10 h at 45 °C. Then the mixture was concentrated and the residue was purified by column chromatography (hexane–EtOAc; 1:1) to provide **4** (1.1 g, 51%) as a pale yellow syrup. $[\alpha]_D^{25}$ 136.4 (*c* 0.64, CHCl₃); ¹H NMR: δ 4.86 (d, 1 H, *J*_{1,2} 3.5 Hz, H-1), 3.78 (m, 1 H, H-5), 3.60 (dd, 1 H, *J*_{gem} 12.2 Hz, H-6a), 3.51 (dd, 1 H, *J*_{2,3} 9.5 Hz, *J*_{3,4} 3.6 Hz, H-3), 3.44, 3.42, and 3.41 (each s, each 3 H, 3 OMe), 3.35 (dd, 1 H, H-2), 3.16 (dd, 1 H, H-6b) 3.08 (dd, 1 H, *J*_{4,5} ~1 Hz, H-4), 2.25 (m, 1 H, cyclohexyl CH), 1.80–1.50 and 1.20–0.70 (m, 10 H, cyclohexyl CH₂); ¹³C NMR: δ 97.3 (C-1), 79.1 (C-3), 77.1 (C-2), 70.3 (C-5), 58.6, 57.8 and 55.2 (3 OMe), 56.8 (cyclohexyl CH) 53.7 (C-4), 52.2 (C-6), 34.5, 33.6, 25.8, 25.2, 25.0 (5 cyclohexyl CH₂); MS: Calcd. for: C₁₅H₂₈N₄O₄ 328, found: 329 [M+H]⁺; HRMS: [M+H]⁺ calcd. for 329.2189, found: 329.2191.

3.5. Methyl 6-azido-4-benzylamino-4,6-dideoxy-2,3-di-*O*-methyl- α -D-galactopyranoside (5)

Compound **3** (1.61 g, 6.7 mmol) was converted into the 4-*O*-triflate intermediate as described for compound **4**. A solution of benzylamine (6 mL) in DMF (20 mL) was added to the triflate intermediate and the mixture was stirred for 10 h at 45 °C. Then the mixture was concentrated and the residue was purified by column chromatography (hexane–EtOAc; 1:1) to give **5** (1.67 g, 76%) as a pale yellow syrup: $[\alpha]_D^{25}$ 117.2 (*c* 0.8, CHCl₃); ¹H NMR: δ 7.40–7.20 (m, 5 H, aromatic), 4.95 (d, 1 H, $J_{1,2}$ 3.7 Hz, H-1), 3.85 (m, 3 H, H-5 and benzyl CH₂), 3.70 and 3.22 (each dd, 2 H, $J_{5,6}$ 8.8 and 4.2 Hz, J_{gem} 12.5 Hz, H-6a), 3.60 (dd, 1 H, $J_{2,3}$ 9.9 Hz, $J_{3,4}$ 4.2 Hz, H-3), 3.48, 3.44 and 3.28 (each s, each 3 H, 3 OMe), 3.43 (dd, 1 H, H-2), 3.10 (dd, 1 H, $J_{4,5}$ 1.3 Hz, H-4); ¹³C NMR: δ 140.1, 128.3, and 127.1 (aromatic), 97.5 (C-1), 79.4 (C-3), 77.1 (C-2), 70.2 (C-5), 58.6, 57.4 and 55.2 (3 OMe), 55.4 (C-4), 54.4 (benzyl CH₂), 52.3 (C-6); MS: Calcd. for: C₁₆H₂₄N₄O₄ 336, found: 337 [M+H]⁺. Anal. Calcd for C₁₆H₂₄N₄O₄: C, 57.13; H, 7.19. Found: C, 57.07; H, 7.18.

3.6. Methyl 4-cyclohexylamino-4,6-dideoxy-2,3-di-*O*-methyl-6-(*N*'-phenyl)thioureido- α -D-galactopyranoside (6)

Propanedithiol (2.0 mL) was added to a solution of **4** (0.8 g, 2.4 mmol) in MeOH (20 mL) at rt and the mixture was stirred for 48 h at rt. When TLC (hexane–EtOAc, 1:1) showed the formation of the 6-amino derivative the mixture was filtered, the filtrate was evaporated and the residue was purified by column chromatography (CH₂Cl₂–MeOH–water; 8:5:1) to afford the amino derivative (0.65 g). Phenyl isothiocyanate (400 μ L) was added to a solution of the amino derivative (650 mg) in MeOH (10 mL) at rt. The mixture was stirred for 4 h then concentrated. After column chromatography (CH₂Cl₂–MeOH–water; 8:5:1) of the residue a white solid was obtained, which was recrystallized from EtOAc to yield **6** (450 mg, 42 %, over two steps): m.p 160–162 °C; $[\alpha]_D^{25}$ 84.7 (*c* 0.54, CHCl₃); ¹H NMR: δ 8.36 (bs, 1 H, NH), 7.42–7.20 (m, 5 H, aromatic), 4.80 (d, 1 H, $J_{1,2}$ 3.7 Hz, H-1), 4.32 (bs, 1 H, H-6a), 3.86 (m, 1 H, H-5), 3.57 (dd, 1 H, $J_{2,3}$ 10.2 Hz, $J_{3,4}$ 4.7 Hz, H-3), 3.48 (m, 1 H, H-6b), 3.46, 3.42, and 3.20 (each s, each 3 H, 3 OMe), 3.30 (dd, 1 H, H-2), 3.14 (dd, 1 H, H-4), 2.28 (m, 1 H, cyclohexyl CH), 1.80–1.50 and 1.20–0.70 (m, 10 H, cyclohexyl CH₂); ¹³C NMR: δ 180.0 (C=S), 136.3, 129.8, 126.8, and 125.0 (aromatic), 97.4 (C-1), 79.0 (C-3), 77.1 (C-2), 68.0 (C-

5), 58.5, 58.0 and 54.9 (3 OMe), 56.9 (cyclohexyl CH) 54.5 (C-4), 47.2 (C-6), 34.0, 33.3, 25.7, 25.0, 24.9 (5 cyclohexyl CH₂); MS: Calcd. for: C₂₂H₃₅N₃O₄S 437, found: 438 [M+H]⁺. Anal. Calcd for C₂₂H₃₅N₃O₄S: C, 60.38; H, 8.06. Found: C, 60.42; H, 8.04.

3.7. Methyl 4-cyclohexylamino-4,6-dideoxy-2,3-di-*O*-methyl-6-(*N*'-3,5-bis(trifluoromethyl)phenyl)thioureido- α -D-galactopyranoside (7)

Compound **4** (0.8 g, 2.4 mmol) was converted into the 6-amino derivative as described for compound **6**. 3,5-Bis(trifluoromethyl)phenyl isothiocyanate (400 μ L) was added to a solution of the 6-amino derivative (0.65 g) in MeOH (10 mL) at rt. The mixture was stirred for 4 h then concentrated and the product was isolated after column chromatography (hexane–EtOAc; 1:2) as a white solid. The solid was recrystallized from EtOAc to yield **7** (530 mg, 35 %, over two steps): m.p. 189–191 °C; [α]_D²⁵ 39.7 (*c* 0.51, CHCl₃); ¹H NMR: δ 10.18 (bs, 1 H, 6-NH), 8.95 (bs, 1 H, NH), 7.84 (s, 2 H, aromatic) 7.68 (s, 1 H, aromatic), 4.95 (d, 1 H, *J*_{1,2} 3.5 Hz, H-1), 4.40 (m, 1 H, H-6a), 3.96 (m, 1 H, H-5), 3.65 (dd, 1 H, *J*_{2,3} 10.4 Hz, *J*_{3,4} 4.7 Hz, H-3), 3.55, 3.46 and 3.44 (each s, each 3 H, 3 OMe), 3.45 (m, 1 H, H-6b), 3.28 (dd, 1 H, H-2), 3.22 (dd, 1 H, H-4), 2.37 (m, 1 H, cyclohexyl CH), 1.60–1.44 and 1.20–0.50 (m, 10 H, cyclohexyl CH₂); ¹³C NMR: δ 178.8 (C=S), 139.5 (aromatic quaterner), 132.8 (q, 2 C, ²*J*_{C,F} 33 Hz, C-3'' and C-5''), 122.9 (q, 2 C, ¹*J*_{C,F} 271 Hz, 2 CF₃), 122.8 (m, 2 C, C-2'' and C-6''), 118.4 (m, 1 C, C-4''), 97.7 (C-1), 79.4 (C-3), 77.2 (C-2), 65.5 (C-5), 58.7, 58.6 and 55.5 (3 OMe), 57.0 (cyclohexyl CH) 54.3 (C-4), 49.3 (C-6), 33.2, 32.8, 25.5, 24.8, 24.6 (5 cyclohexyl CH₂); MS: Calcd. for: C₂₄H₃₃F₆N₃O₄S 573, found: 574 [M+H]⁺. Anal. Calcd for C₂₄H₃₃F₆N₃O₄S: C, 50.25; H, 5.80. Found: C, 50.31; H, 5.82.

3.8. Methyl 4-benzylamino-4,6-dideoxy-2,3-di-*O*-methyl-6-(*N*'-phenyl)thioureido- α -D-galactopyranoside (8)

Triphenylphosphine (1.2 g, 4.6 mmol) was added to a solution of **5** (1.0 g, 3.0 mmol) in THF (20 mL) at rt and the mixture was stirred for 2 h at 80 °C. When TLC (hexane–EtOAc; 1:1) showed the absence of the starting material water (2 mL) was added to the mixture and the stirring was continued for 4 h at 80 °C. The mixture was concentrated, the residue was purified by column chromatography (CH₂Cl₂–MeOH–water 8:5:1) affording the 6-amino derivative (0.7 g). Phenyl isothiocyanate (225 μ L) was added to a solution the 6-

amino-derivative (485 mg) in MeOH (10 mL) at rt. The mixture was stirred for 24 h then concentrated and the product was obtained after column chromatography (CH₂Cl₂–MeOH–water 8:5:1) as a white solid. The solid was recrystallized from CH₂Cl₂/hexane to yield **8** (281 mg, 31%, over two steps) as white crystals: mp 100–102 °C; $[\alpha]_D^{25}$ 116.9 (*c* 0.65, CHCl₃); ¹H NMR: δ 8.18 (s, 1 H, NHPh), 7.40 – 7.18 (m, 10 H, aromatic), 6.92 (d, 1 H, 6-NH), 4.78 (d, 1 H, *J*_{1,2} 3.5 Hz, H-1), 4.34 (bs, 1 H, H-6a), 3.89 (m, 1 H, H-5), 3.80 (ABq, 2 H, benzyl CH₂), 3.68 (m, 1 H, H-6b), 3.59 (dd, 1 H, *J*_{2,3} 10.3 Hz, *J*_{3,4} 3.6 Hz, H-3), 3.44, 3.25 and 3.17 (each s, each 3 H, 3 OMe), 3.35 (dd, 1 H, H-2), 3.13 (dd, 1 H, H-4), 1.66 (bs, 1 H, 4-NH); ¹³C NMR: δ 180.4 (C=S), 139.7, 136.1, 129.9, 128.4, 127.1 and 125.2 (aromatic), 97.6 (C-1), 79.0 (C-3), 77.0 (C-2), 68.6 (C-5), 58.7, 57.4 and 55.0 (3 OMe), 56.2 (C-4), 54.9 (benzyl CH₂), 47.1 (C-6); MS: Calcd. for: C₂₃H₃₁N₃O₄S 445, found: 446 [M+H]⁺. Anal. Calcd for C₂₃H₃₁N₃O₄S: C, 62.00; H, 7.01. Found: C, 62.07; H, 7.02.

3.9. Methyl 4-benzylamino-4,6-dideoxy-2,3-di-*O*-methyl-6-(*N*'-3,5-bis(trifluoromethyl)phenyl)thioureido- α -D-galactopyranoside (**9**)

Compound **5** (1.0 g 3.0 mmol) was converted into the 6-amino derivative as described for **8**. 3,5-Bis(trifluoromethyl)phenyl isothiocyanate (350 μ L) was added to a solution of the 6-amino derivative (497 mg) in MeOH (10 mL) at rt. The mixture was stirred for 10 min, during this time a light brown precipitate was formed. The solid was filtered and was purified by recrystallization from EtOAc/hexane to afford **9** (868 mg, 70%, over two steps) as white crystals: mp 180–182 °C; $[\alpha]_D^{25}$ 69.9 (*c* 0.89, CHCl₃); ¹H NMR: δ 9.28 (bs, 1 H, NH), 8.66 (bs, 1 H, NH), 7.50 – 7.40 (m, 8 H, aromatic) 4.90 (d, 1 H, *J*_{1,2} 3.5 Hz, H-1), 4.40 (m, 1 H, H-6a), 4.00 (m, 1 H, H-5), 3.84 and 3.55 (each m, 2 H, benzyl CH₂), 3.70 (dd, 1 H, *J*_{2,3} 10.2 Hz, *J*_{3,4} 4.7 Hz, H-3), 3.65 (m, 1 H, H-6b), 3.51, 3.41 and 3.40 (each s, each 3 H, 3 OMe), 3.34 (dd, 1 H, H-2), 3.22 (dd, 1 H, H-4), 2.00 (bs, 1 H, 4-NH); ¹³C NMR: δ 179.6 (C=S), 139.5 (aromatic quaterner), 132.8 (C-3'' and C-5''), 129.2, 128.8, 128.1, and 127.6 (aromatic), 123.2 (q, 2 C, ¹*J*_{C,F} 271 Hz, 2 CF₃), 121.4 (m, 2 C, C-2'' and C-6''), 114.9 (m, 1 C, C-4''), 98.0 (C-1), 79.1 (C-3), 77.9 (C-2), 66.1 (C-5), 59.4 (C-4), 59.0, 58.4 and 55.8 (3 OMe), 55.7 (benzyl CH₂), 49.1 (C-6); MS: Calcd. for: C₂₅H₂₉F₆N₃O₄S 581, found: 582 [M+H]⁺. Anal. Calcd for C₂₅H₂₉F₆N₃O₄S: C, 51.63; H, 5.03. Found: C, 51.51; H, 5.00.

3.10. Methyl 4-*O*-benzoyl-6-deoxy-2,3-di-*O*-methyl-6-piperidino- α -D-glucopyranoside (10)

Piperidine (720 μ L, 7.3 mmol) was added to a solution of **1** (1.12 g, 2.88 mmol) in dry DMF (5 mL) and the mixture was stirred for 50 h at 70 °C. Then the mixture was allowed to cool to r.t., it was diluted with toluene (100 mL) and washed with water (2×30 mL), the organic layer was dried over MgSO_4 , filtered, and concentrated. Column chromatography (toluene–acetone; 3:1) of the residue afforded **10** (1.01 g, 90%) as a syrup: $[\alpha]_D^{25}$ 80.2 (c 0.63, CHCl_3); ^1H NMR: δ 8.05, 7.55 and 7.42 (m, 5 H, aromatic), 5.00 (dd, 1 H, $J_{3,4}$ 9.4 Hz, $J_{4,5}$ 9.9 Hz, H-4), 4.86 (d, 1 H, $J_{1,2}$ 3.5 Hz, H-1), 4.03 (m, 1 H, H-5), 3.66 (dd, 1 H, $J_{2,3}$ 9.4 Hz, H-3), 3.51, 3.46 and 3.43 (each s, each 3 H, 3 OMe), 3.31 (dd, 1 H, H-2), 2.50 and 2.36 (each dd, 2 H, J_{gem} 13.4 Hz, H-6), 2.33, 1.46 and 1.30 (each m, 10 H, 5 piperidine CH_2); ^{13}C NMR: δ 165.5 (C=O), 133.1, 129.7 and 128.3 (aromatic), 97.5 (C-1), 81.4 (C-2), 81.0 (C-3), 73.2 (C-4), 66.9 (C-5), 60.8, 59.2 and 55.5 (3 OMe), 60.1 (C-6), 55.1, 25.7 and 24.1 (5 piperidine CH_2); MS: Calcd. for: $\text{C}_{21}\text{H}_{31}\text{NO}_6$ 393, found: 394 $[\text{M}+\text{H}]^+$. Anal. Calcd for $\text{C}_{21}\text{H}_{31}\text{NO}_6$: C, 64.10; H, 7.94. Found: C, 64.03; H, 7.92.

3.11 Methyl 6-deoxy-2,3-di-*O*-methyl-6-piperidino- α -D-glucopyranoside (11)

NaOMe (50 mg) was added to a solution of **10** (1.0 g, 2.54 mmol) in dry MeOH (20 mL) at r.t., then the mixture was stirred for 2 h at reflux. The mixture was concentrated and the residue was purified by column chromatography (CH_2Cl_2 – MeOH ; 95:5 \rightarrow 8:2) to give **11** (618 mg, 85%) as a colorless syrup: $[\alpha]_D^{25}$ 73.4 (c 0.63, CHCl_3); ^1H NMR: δ 4.68 (d, 1 H, $J_{1,2}$ 3.5 Hz, H-1), 3.60 (m, 1 H, H-5), 3.56, 3.42 and 3.32 (each s, each 3 H, 3 OMe), 3.40 (m, 2 H, H-3 and H-4), 3.10 (dd, 1 H, H-2), 2.60 (m, 2 H, J_{gem} 12.3 Hz, H-6), 2.55, 2.30, 1.50 and 1.33 (each m, 10 H, 5 piperidine CH_2); ^{13}C NMR: δ 97.5 (C-1), 82.0 (C-3), 81.0 (C-2), 71.1 (C-4), 64.4 (C-5), 63.1 (C-6), 60.8, 58.6 and 55.0 (3 OMe), 55.4, 25.7 and 23.3 (5 piperidine CH_2); MS: Calcd. for: $\text{C}_{14}\text{H}_{27}\text{NO}_5$ 289, found: 290 $[\text{M}+\text{H}]^+$, 312 $[\text{M}+\text{Na}]^+$. Anal. Calcd for $\text{C}_{14}\text{H}_{27}\text{NO}_5$: C, 58.11; H, 9.40. Found: C, 58.10; H, 9.37.

3.12. Methyl 4-azido-4,6-dideoxy-2,3-di-*O*-methyl-6-piperidino- α -D-galactopyranoside (12)

A solution of TiF_2O (1.89 mL, 11.3 mmol) in CH_2Cl_2 (5 mL) was added to a solution of **11** (2.16 g 7.5 mmol) in a mixture of pyridine (3.6 mL) and CH_2Cl_2 (50 mL) at 0 °C and the mixture was stirred for 2 h at 0 °C. Sodium azide (980 mg) in DMF (50 mL) was added to the mixture and stirring was continued for 72 h at 45 °C. Then the mixture was concentrated and the residue was purified by column chromatography (CH_2Cl_2 –MeOH, 95:5) to yield **12** (700 mg, 30%) as a pale yellow syrup: $[\alpha]_D^{25}$ 104.8 (*c* 0.65, CHCl_3); ^1H NMR δ : 4.72 (d, 1 H, $J_{1,2}$ 3.4 Hz, H-1), 4.10 (dd, 1 H, $J_{3,4}$ 2.3 Hz $J_{4,5}$ <1 Hz, H-4), 3.90 (m, 1 H, H-5), 3.69 (dd, 1 H, $J_{2,3}$ 9.8 Hz, H-3), 3.58, 3.56 and 3.40 (each s, each 3 H, 3 OMe), 3.50 (m, 1 H, H-2), 2.50 (m, 6 H, H-6 and 2 piperidine CH_2), 1.60 and 1.40 (each m, 6 H, 3 piperidine CH_2); ^{13}C NMR: δ 98.2 (C-1), 79.8 (C-3), 78.1 (C-2), 66.3 (C-5), 61.7 (C-4), 59.7 (C-6), 59.4, 58.4 and 55.8 (3 OMe), 55.6, 26.2 and 24.4 (5 piperidine CH_2); MS: Calcd. for: $\text{C}_{14}\text{H}_{26}\text{N}_4\text{O}_4$ 314, found: 315 $[\text{M}+\text{H}]^+$, 332 $[\text{M}+\text{NH}_4]^+$. Anal. Calcd for $\text{C}_{14}\text{H}_{26}\text{N}_4\text{O}_4$: C, 53.49; H, 8.34. Found: C, 53.42; H, 8.32.

3.13. Methyl 4,6-dideoxy-2,3-di-*O*-methyl-6-piperidino-4-(*N'*-phenyl)thioureido- α -D-galactopyranoside (**13**)

Propanedithiol (200 μL) was added to a solution of **12** (300 mg, 0.95 mmol) in MeOH (5 mL) at rt and the mixture was stirred for 72 h at 50 °C. When TLC (CH_2Cl_2 –MeOH, 95:5) showed the formation of the 4-amino derivative, the mixture was filtered and the filtrate was concentrated. The residue was dissolved in MeOH (10 mL) and phenyl isothiocyanate (200 μL) was added to the solution. The mixture was stirred for 8 h at rt, then it was concentrated and the residue was purified by column chromatography (CH_2Cl_2 –MeOH; 95:5) to afford **13** (280 mg, 69 % over two steps) as a syrup: $[\alpha]_D^{25}$ 122.5 (*c* 0.59, CHCl_3); ^1H NMR: δ 8.78 (bd, 1 H, NH), 7.45 – 7.20 (m, 5 H, aromatic), 6.51 (bs, 1 H, NH), 5.30 (bd, 1 H, H-4), 4.80 (d, 1 H, $J_{1,2}$ 3.0 Hz, H-1), 4.10 (m, 1 H, H-5), 3.67 (dd, 1 H, $J_{2,3}$ 10.3 Hz, $J_{3,4}$ 4.4 Hz, H-3), 3.53, 3.50 and 3.38 (each s, each 3 H, 3 OMe), 3.11 (m, 1 H, H-2), 2.66 (dd, 1 H, H-6a), 2.46 (m, 5 H, H-6b and 2 piperidine CH_2), 1.58 and 1.42 (each m, 6 H, 3 piperidine CH_2); ^{13}C NMR: δ 181.5 (C=S), 136.7, 129.6, 126.5 and 126.6 (aromatic), 97.6 (C-1), 78.2 (C-3), 77.6 (C-2), 65.9 (C-5), 59.1 (C-6), 58.9, 58.1 and 55.6 (3 OMe), 54.5 (C-4), 54.9, 25.3 and 23.7 (5 piperidine CH_2); MS: Calcd. for: $\text{C}_{21}\text{H}_{33}\text{N}_3\text{O}_4\text{S}$ 423, found: 424 $[\text{M}+\text{H}]^+$. Anal. Calcd for $\text{C}_{21}\text{H}_{33}\text{N}_3\text{O}_4\text{S}$: C, 59.55; H, 7.85. Found: C, 59.58; H, 7.89.

3.14. Methyl 4,6-*O*-benzylidene-2-deoxy-2-piperidino- α -D-altropyranoside (**15**)

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Piperidine (6.73 mL) and LiClO₄ (3.62 g) were added to a solution of **14** (4.5 g, 17.0 mmol) in MeCN (50 mL) at rt and the mixture was stirred for 24 h at 90 °C. Then the mixture was concentrated, the residue was redissolved in EtOAc (300 mL) and washed with water (3 × 150 mL), the organic layer was dried, filtered and concentrated. After column chromatography (CH₂Cl₂–MeOH; 95:5) **15** (5.7 g, 95 %) was obtained as white crystals: mp 83–85 °C (hexane/EtOAc), lit¹¹ mp 117–118 °C; $[\alpha]_D^{25}$ 74.3 (c 0.64, CHCl₃); lit¹¹ $[\alpha]_D^{25}$ 90.8 (c 1.3, CH₂Cl₂); ¹H NMR: δ 7.54–7.32 (m, 5 H, aromatic), 5.64 (s, 1 H, -CHPh), 4.80 (s, 1 H, H-1), 4.32 (dd, 1 H, *J*_{gem} 10.1 Hz, H-6a), 4.13 (m, 2 H, H-3 and H-5), 3.90 (dd, 1 H, *J*_{3,4} 2.9 Hz, *J*_{4,5} 9.8 Hz, H-4), 3.80 (dd, 1 H, H-6b), 3.40 (s, 3 H, OMe), 3.18 (d, 1 H, *J*_{3,OH} 4.7 Hz, 3-OH), 2.84 (d, 1 H, *J*_{2,3} 2.1 Hz, H-2), 2.70 and 2.55 (each m, each 2 H, 2 -CH₂-), 1.60 and 1.45 (m, 6 H, -CH₂-); ¹³C NMR: δ 137.4, 129.1, 128.2 and 126.2 (aromatic), 102.1 (-CHPh), 101.2 (C-1), 77.8 (C-4), 69.4 (C-6), 67.8 (C-2), 65.6 and 57.7 (C-3 and C-5), 55.3 (OMe), 51.8, 26.5 and 24.2 (5 -CH₂); MS: Calcd. for: C₁₉H₂₇NO₅ 349, found: 350 [M+H]⁺.

3.15 Methyl 4,6-*O*-benzylidene-2-deoxy-2-morpholino- α -D-altropyranoside (**16**)

Morpholine (5.9 mL) and LiClO₄ (3.62 g) were added to a solution of **14** (4.5 g, 17.0 mmol) in MeCN (50 mL) at rt and the mixture was stirred for 24 h at 90 °C. Then the mixture was concentrated and the residue was taken up in EtOAc (300 mL) and washed with water (3 × 150 mL), the organic layer was dried, filtered and concentrated. Purification of the residue by column chromatography (CH₂Cl₂–MeOH; 95:5) afforded **16** (5.0 g, 84 %) as white crystals: mp 117–119 °C (hexane), lit¹¹ mp 118–119 °C; $[\alpha]_D^{25}$ 73.2 (c 0.71, CHCl₃); lit¹¹ $[\alpha]_D^{25}$ 71.7 (c 1.2, CH₂Cl₂); ¹H NMR: δ 7.54–7.32 (m, 5 H, aromatic), 5.64 (s, 1 H, -CHPh), 4.83 (s, 1 H, H-1), 4.32 (dd, 1 H, *J*_{gem} 10.1 Hz, H-6a), 4.16 (m, 2 H, H-3 and H-5), 3.92 (dd, 1 H, *J*_{3,4} 3.1 Hz, *J*_{4,5} 9.8 Hz, H-4), 3.79 (dd, 1 H, H-6b), 3.70 (t, 4 H, -CH₂OCH₂-), 3.42 (s, 3 H, OMe), 3.17 (d, 1 H, *J*_{3,OH} 6.6 Hz, 3-OH), 2.79 (d, 1 H, *J*_{2,3} 1.9 Hz, H-2), 2.70 and 2.60 (each m, each 2 H, 2 -CH₂-); ¹³C NMR: δ 137.2, 129.0, 128.2 and 126.2 (aromatic), 102.2 (-CHPh), 100.0 (C-1), 77.4 (C-4), 69.2 (C-6), 67.2 (-CH₂OCH₂-), 67.0 (C-2), 65.9 and 57.8 (C-3 and C-5), 55.4 (OMe), 51.1 (2 × -CH₂); MS: Calcd. for: C₁₈H₂₅NO₆ 351, found: 352 [M+H]⁺.

3.16. Methyl 3-azido-4,6-*O*-benzylidene-2,3-dideoxy-2-piperidino- α -D-mannopyranoside (**17**)

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Diisopropyl azodicarboxylate (1.33 mL, 6.8 mmol) was added to a solution of **15** (2.0 g, 5.73 mmol) and PPh₃ (1.79 g, 6.87 mmol) in THF (50 mL) at 0 °C and the mixture was stirred for 20 min at 0 °C. Then diphenylphosphoryl azide (1.48 mL, 6.86 mmol) in THF (12 mL) was added and the mixture was stirred for 24 h at rt. Then the mixture was concentrated, the residue was taken up in EtOAc (300 mL) and washed with sat. NaHCO₃ solution (150 mL), the organic layer was dried, filtered and concentrated. Column chromatography (CH₂Cl₂–EtOAc; 95:5) of the residue followed by recrystallization from hexane/EtOAc afforded **17** (1.27 g, 60 %) as white crystals: mp 161–163 °C; $[\alpha]_D^{25}$ 17.8 (*c* 0.89, CHCl₃); ¹H NMR: δ 7.55–7.33 (m, 5 H, aromatic), 5.60 (s, 1 H, -CHPh), 4.70 (s, 1 H, H-1), 4.32 (dd, 1 H, *J*_{gem} 9.9 Hz, H-6a), 4.20 (m, 1 H, H-5), 4.13 (m, 1 H, H-3), 4.01 (dd, 1 H, *J*_{3,4} 3.8 Hz, *J*_{4,5} 9.8 Hz, H-4), 3.74 (dd, 1 H, H-6b), 3.38 (s, 3 H, OMe), 2.86 (d, 1 H, *J*_{2,3} 1.2 Hz, H-2), 2.72 and 2.55 (each m, each 2 H, 2 -CH₂-), 1.60 and 1.45 (m, 6 H, -CH₂-); ¹³C NMR: δ 137.1, 129.1, 128.3 and 126.1 (aromatic), 102.2 (-CHPh), 101.3 (C-1), 77.7 (C-4), 69.4 (C-6), 67.4 (C-2), 58.0 (C-5), 56.0 (C-3), 55.2 (OMe), 51.7, 26.5 and 24.2 (5 -CH₂); MS: Calcd. for: C₁₉H₂₆N₄O₄ 374, found: 375 [M+H]⁺. Anal. Calcd for C₁₉H₂₆N₄O₄: C, 60.95; H, 7.00. Found: C, 60.99; H, 7.01.

3.17. Methyl 3-azido-4,6-*O*-benzylidene-2,3-dideoxy-2-morpholino- α -D-mannopyranoside (**18**)

Compound **16** (2.0 g, 5.73 mmol) was converted into the azido derivative as described for **17**. Column chromatography (CH₂Cl₂–EtOAc, 95:5) followed by crystallization from hexane/EtOAc afforded **18** (1.49 g, 69 %) as white crystals: mp 164–166 °C; $[\alpha]_D^{25}$ 26.2 (*c* 0.62, CHCl₃); ¹H NMR: δ 7.54–7.34 (m, 5 H, aromatic), 5.61 (s, 1 H, -CHPh), 4.72 (s, 1 H, H-1), 4.30 (dd, 1 H, *J*_{gem} 10.0 Hz, H-6a), 4.21 (m, 1 H, H-5), 4.11 (m, 1 H, H-3), 4.04 (dd, 1 H, *J*_{3,4} 3.6 Hz, *J*_{4,5} 9.2 Hz, H-4), 3.73 (dd, 1 H, H-6b), 3.70 (t, 4 H, -CH₂OCH₂-), 3.38 (s, 3 H, OMe), 2.81 (d, 1 H, *J*_{2,3} 1.3 Hz, H-2), 2.75 and 2.64 (each m, each 2 H, 2 -CH₂-); ¹³C NMR: δ 137.0, 129.2, 128.3 and 126.1 (aromatic), 102.3 (-CHPh), 100.0 (C-1), 77.4 (C-4), 69.2 (C-6), 67.3 (-CH₂OCH₂-), 66.5 (C-2), 58.1 (C-5), 56.5 (C-3), 55.4 (OMe), 50.9 (2 -CH₂); MS: Calcd. for: C₁₈H₂₄N₄O₅ 376, found: 377 [M+H]⁺. Anal. Calcd for C₁₈H₂₄N₄O₅: C, 57.44; H, 6.43. Found: C, 57.57; H, 6.44.

3.18. Methyl 4,6-*O*-benzylidene-2,3-dideoxy-2-piperidino-3-(*N'*-phenyl)thioureido- α -D-mannopyranoside (**19**)

Triphenylphosphine (1.51 g, 5.7 mmol) was added to a solution of **17** (1.2 g, 3.2 mmol) in THF (15 mL) at rt and the mixture was stirred for 2 h at 80 °C. When TLC (hexane:EtOAc; 1:1) showed the absence of the starting material water (0.75 mL) was added to the mixture and the stirring was continued for 4 h at 80 °C. Evaporation of the solvent and column chromatography (CH₂Cl₂–MeOH; 98:2) of the residue afforded the 3-amino derivative (900 mg). Phenyl isothiocyanate (300 μ L) was added to a solution of the amino derivative (600 mg) in MeOH (10 mL) at rt. The mixture was stirred for 30 min then concentrated and the product was isolated by column chromatography (CH₂Cl₂–MeOH; 98:2). Compound **19** (733 mg, 71%) was obtained as a syrup: $[\alpha]_D^{25}$ 18.7 (*c* 0.82, CHCl₃); ¹H NMR: δ 8.2 (bs, 1 H, NH), 7.80 – 7.00 (m, 10 H, aromatic), 5.65 (s, 1 H, -CHPh), 4.76 (s, 1 H, H-1), 4.20 (m, 2 H, H-4 and H-6a), 3.79 (dd, 1 H, H-6b), 3.65 (bs, 1 H, H-5), 3.33 (bs, 3 H, OMe), 2.80 – 2.50 (m, 4 H, H-2, H-3 and 2 -CH₂-), 1.58 and 1.45 (m, 6 H, -CH₂-); ¹³C NMR: δ 181.0 (C=S), 137.6, 137.1, 131.9, 131.8, 131.7, 128.4, and 126.0 (aromatic), 101.6 (-CHPh), 99.4 (C-1), 76.0 (C-4), 69.2 (C-6), 66.2 (C-2), 59.4 (C-5), 55.6 (OMe), 52.0 (2 -CH₂), 51.8 (C-3), 26.3 and 24.1 (3 -CH₂); MS: Calcd. for: C₂₆H₃₃N₃O₄S 483, found: 484 [M+H]⁺. Anal. Calcd for C₂₆H₃₃N₃O₄S: C, 64.57; H, 6.88. Found: C, 64.37; H, 6.91.

3.19. Methyl 4,6-*O*-benzylidene-2,3-dideoxy-2-piperidino-3-(*N'*-3,5-bis(trifluoromethyl)phenyl)thioureido- α -D-mannopyranoside (**20**)

Compound **17** was converted into the 3-amino derivative as described for compound **19**. 3,5-Bis(trifluoromethyl)phenyl isothiocyanate (470 μ L) was added to a solution of the 3-amino derivative (600 mg) in MeOH (10 mL) at rt. The mixture was stirred for 30 min then concentrated. Column chromatography (CH₂Cl₂–EtOAc; 98:2) of the residue provided **20** (900 mg, 81%) as a syrup: $[\alpha]_D^{25}$ –41.7 (*c* 0.69, CHCl₃); ¹H NMR: δ 8.76 (bs, 1 H, NH), 7.70 – 7.30 (m, 8 H, aromatic), 5.70 (s, 1 H, -CHPh), 4.86 (s, 1 H, H-1), 4.30 (m, 2 H, H-4 and H-6a), 4.10 (m, 1 H, H-5), 3.82 (dd, 1 H, H-6b), 3.40 (bs, 3 H, OMe), 2.80 – 2.55 (m, 4 H, H-2, H-3 and 2 -CH₂-), 1.58 and 1.45 (m, 6 H, -CH₂-); ¹³C NMR: δ 183.2 (C=S), 136.5 (aromatic), 131.0 (C-3'' and C-5''), 128.5, 128.3 and 128.1 (aromatic), 122.8 (q, 2 C, ¹J_{C,F} 271 Hz, 2 CF₃), 123.1 (m, 2 C, C-2'' and C-6''), 102.8 (-CHPh), 99.3 (C-1), 77.5 (C-4), 69.1 (C-6), 66.4 (C-2),

59.8 (C-5), 55.5 (OMe), 53.1 (C-3), 52.0 (2 -CH₂), 26.4 and 24.1 (3 -CH₂); MS: Calcd. for: C₂₈H₃₁F₆N₃O₄S 619, found: 620 [M+H]⁺. Anal. Calcd for C₂₈H₃₁F₆N₃O₄S: C, 54.28; H, 5.04. Found: C, 54.16; H, 5.04.

3.20. Methyl 4,6-*O*-benzylidene-2,3-dideoxy-2-morpholino-3-(*N*'-phenyl)thioureido- α -D-mannopyranoside (**21**)

Compound **18** (2.46 g, 6.5 mmol) was converted into the 3-amino derivative (1.34 g) as described for **19**. Phenyl isothiocyanate (130 μ L) was added to a solution of the crude amino derivative (251 mg) in MeOH (8 mL) at rt. The mixture was stirred for 30 min, the product, which formed as a precipitate, was filtered and was recrystallized from EtOAc/hexane to afford **21** (167 mg, 29% over two steps) as white crystals: mp 192–193 °C; $[\alpha]_D^{25}$ 45.9 (*c* 0.84, CHCl₃); ¹H NMR: δ 8.40 (bs, 1 H, NH), 7.50 – 7.20 (m, 10 H, aromatic), 5.65 (s, 1 H, -CHPh), 4.67 (s, 1 H, H-1), 4.20 (m, 2 H, H-4 and H-6a), 3.78 (t, 1 H, H-6b), 3.70 (t, 4 H, -CH₂OCH₂-), 3.60 (bs, 1 H, H-5), 3.10 (s, 3 H, OMe), 2.80 and 2.60 (m, 6 H, H-2, H-3 and 2 -CH₂-); ¹³C NMR: δ 180.6 (C=S), 137.0, 129.4, 128.7, 128.0, 125.9, and 125.1 (aromatic), 101.6 (-CHPh), 98.2 (C-1), 75.2 (C-4), 69.0 (C-6), 67.2 (-CH₂OCH₂-), 65.4 (C-2), 59.5 (C-5), 55.7 (OMe), 51.4 (C-3), 51.2 (2 -CH₂-); MS: Calcd. for: C₂₅H₃₁N₃O₅S 485, found: 486 [M+H]⁺, 508 [M+Na]⁺. Anal. Calcd for C₂₅H₃₁N₃O₅S: C, 61.83; H, 6.43. Found: C, 61.87; H, 6.54.

3.21. Methyl 4,6-*O*-benzylidene-2,3-dideoxy-2-morpholino-3-(*N*'-3,5-bis(trifluoromethyl)phenyl)thioureido- α -D-mannopyranoside (**22**)

Compound **18** (2.46 g, 6.5 mmol) was converted into the 3-amino derivative (1.34 g) as described for **19**. 3,5-Bis(trifluoromethyl)phenyl isothiocyanate (720 μ L) was added to a solution of the crude amino derivative (920 mg) in MeOH (10 mL) at rt. The mixture was stirred for 30 min then concentrated. Column chromatography (CH₂Cl₂–EtOAc; 98:2→95:5) of the residue afforded **22** (733 mg, 27%) as a syrup: $[\alpha]_D^{25}$ –23.4 (*c* 0.74, CHCl₃); ¹H NMR: δ 8.70 (bs, 1 H, NH), 7.50 – 7.10 (m, 8 H, aromatic), 5.70 (s, 1 H, -CHPh), 4.78 (s, 1 H, H-1), 4.35 (m, 2 H, H-4 and H-6a), 3.81 (dd, 1 H, H-6b), 3.70 (m, 5 H, H-5 and 2 \times -CH₂-), 3.40 (bs, 3 H, OMe), 2.80 – 2.60 (m, 6 H, H-2, H-3 and 2 -CH₂-); ¹³C NMR: δ 183.1 (C=S), 136.2 (aromatic), 130.2 (C-3'' and C-5''), 128.9, 128.6 and 128.3 (aromatic), 122.8 (q, 2 C, ¹J_{C,F} 270

Hz, 2 CF₃), 123.1 (m, 2 C, C-2'' and C-6''), 102.8 (-CHPh), 98.5 (C-1), 77.4 (C-4), 69.0 (C-6), 67.2 (-CH₂OCH₂-), 65.8 (C-2), 59.1 (C-5), 55.6 (OMe), 52.8 (C-3), 51.2 (2 -CH₂); MS: Calcd. for: C₂₇H₂₉F₆N₃O₅S 621, found: 622 [M+H]⁺; HRMS: [M+Na]⁺ calcd. for 644.1624, found: 644.1629.

3.22. General procedure for the Michael addition

Organocatalyst (0.02 mmol) was added to a solution of β-nitrostyrene (0.2 mmol) in CH₂Cl₂ (0.5 mL) under Ar at rt. The mixture was stirred for 5 min, then acetylacetone (0.22 mmol) was added and stirring was continued for 24 h at rt. The mixture was concentrated and the product was isolated by column chromatography (Hexane–EtOAc; 7:3). The ratio of the formed enantiomers was determined by chiral HPLC method: *t*_{major}: 9.3 min *t*_{minor}: 12.5 min.

3.23. (S)-3-(2-Nitro-1-phenylethyl)-pentane-2,4-dione (23)

¹H NMR: δ 7.35–7.15 (m, 5 H, aromatic), 4.62–4.58 (m, 2 H), 4.36 (d, J=10.8 Hz, 1 H), 4.28–4.20 (m, 1 H), 2.30 (s, 3 H), 1.95 (s, 3 H); ¹³C NMR: δ 201.7, 201.0, 136.0, 129.3, 128.5, 128.0, 78.1, 70.7, 42.8, 30.4, 29.5.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at...

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